11 Models of Absolute Risk

Uses, Estimation, and Validation

Mitchell H. Gail, MD, PhD

CONTENTS

1. INTRODUCTION: DEFINITION AND USES OF ABSOLUTE RISK

Individualized absolute risk is the probability that a person with defined risk factors who is free of the disease of interest at age a will be observed to develop the disease over the age interval $(a, a + \tau)$. For example, the chance that a 40-yr-old nulliparous white woman who began menstruating at the age of 14, who has had no breast biopsies, and whose mother had breast cancer, will develop breast cancer by the age of 70 can be calculated as 0.116, or 11.6%, using the Gail model for breast cancer risk *(1)*. In this paper, breast cancer will usually be the disease of interest, but the ideas apply to any disease.

It is important to distinguish absolute risk from relative risk, which is the ratio of the age-specific incidence rate in a woman with given risk factors to that in a woman without risk factors. In the previous example, the woman's relative risk is 2.76 compared to a 40-yr-old woman with no risk factors. Relative risk is useful for studying the association between a risk factor and disease; relative risks can be estimated from retrospective evaluation of risk factors in diseased and non-diseased subjects, namely case-control studies *(2)*. Knowing that a woman's relative risk of disease is 2.76, however, does not by itself define the chance that she will develop the disease over a given time interval, namely the absolute risk.

Absolute risk is influenced by several factors. Age is usually one of the most influential factors, as the risk of diseases such as cancer usually increases sharply with age. The duration of the age interval $(a, a + \tau)$ also affects absolute risk, which increases with increasing duration, τ. The woman's individual risk factors influence absolute risk. Finally, the absolute risk of a disease like breast cancer is reduced by the chance of dying of some other disease before breast cancer develops. Each of these factors needs to be taken into account in calculating individualized absolute risk (*see* subheading 2)..

Absolute risk estimates are useful for medical counseling. For example, a 40-year-old woman whose absolute risk of developing breast cancer in the next 5 yr is 0.5% might be advised to undergo routine annual examinations with mammography, whereas a similar woman with a projected 5-yr risk of 5% might consider taking a preventive agent, such as tamoxifen *(3)* in addition to mammographic surveillance. In making such decisions, one must weigh the various risks and benefits of the proposed intervention. For example, tamoxifen is associated with an increased risk of stroke, pulmonary embolus, deep vein thrombosis, and endometrial cancer *(4)*. A key ingredient for comparing risks and benefits of an intervention such as tamoxifen is an estimate of the absolute risks of the various health outcomes in the presence and absence of the intervention *(3)*. Using such estimates of absolute risk and a

From: Cancer Chemoprevention, Volume 2: Strategies for Cancer Chemoprevention
Edited by: G. J. Kelloff, E. T. Hawk, and C. C. Sigman © Humana Press Inc., Totowa, NJ 2005

categorization of potential adverse events into life-threatening, severe, and other, Gail et al. *(3)* defined categories of women for whom there was good evidence that the benefits of tamoxifen outweighed the risks. Such calculations required absolute risk estimates for each of the potential adverse outcomes.

Absolute risk is also useful in designing prevention trials. If the trial emphasis is on a single endpoint, such as invasive breast cancer, the concept of absolute risk is directly relevant. The power of a survival analysis based on the logrank test to detect a preventive effect in the active intervention arm compared to placebo depends mainly on the total number of events (e.g., invasive breast cancers) that arise during the trial *(5)*. One can estimate the number of events for a given sample size by averaging the risk-factor-specific absolute risks, calculated for trial duration, over the risk factor distribution in the source population, and multiplying the result by the sample size. Conversely, the required sample size can be computed by dividing the required number of events by the average absolute risk.

The design of an intervention study that examines intervention effects on several health outcomes is more complex. For example, Freedman et al. *(6)* proposed various procedures for monitoring the several beneficial and potentially deleterious effects of hormone replacement therapy in the Woman's Health Initiative. Regardless of the procedure chosen, a computation of the absolute risk of each component health outcome is central to understanding the statistical power of such trial designs and to developing procedures for monitoring the trial *(7)*.

2. ESTIMATION OF ABSOLUTE RISK

Follow-up data from a cohort are required to estimate absolute risk. Gail et al. *(1)* studied a cohort of 243,221 white women followed over 5 yr in the Breast Cancer Detection Demonstration Project (BCDDP) to estimate the absolute risk of breast cancer. If risk factors such as family history of breast cancer and age at first live birth had been available for each of these women, one could have cross-classified the women according to such risk factors, and, for each combination of risk factors (including initial age, a), estimated the absolute risk of developing breast cancer in the next 5 yr.

This approach was not applicable for three reasons. First, detailed risk factor information was available only on the subset of 2582 women with breast cancer and 3146 women without breast cancer who participated in a nested case-control study within the cohort. Second, even if detailed risk factor information had been available on all cohort members, data on breast cancer incidence would have been too sparse to yield reliable estimates within many of the risk factor combinations; thus, some modeling of joint effects on relative risk was required. Finally, to make long-term projections of absolute risk with only 5 yr of follow-up, age- and risk-factor-specific risks will be assumed to remain constant over calendar time.

Formula number 5 in reference *(1)* shows how to compute absolute risk in terms of a relative risk function, $r(t)$, a baseline hazard of the disease of interest, $h_1(t)$, and the hazard of mortality from causes of death except the disease of interest, $h_2(t)$. We discuss these quantities next.

2.1. *Relative Risk,* r(t)

Relative risk, $r(t)$, is the ratio of disease risk at age t for a woman with risk factors $X(t)$ at age t to the risk for a woman whose risk factors are at their lowest ("baseline") level at age t. The relative risk factor in Gail et al. depended on age at menarche, age at first live birth, number of affected first-degree relatives, and number of previous breast biopsies. In projecting risk, it was assumed that these factors remained constant at their values determined at the age $t=a$ of the initial consultation, but, using the same formulas, risk projection could be altered to take changes in these risk factors into account. Relative risk function $r(t)$ can be estimated from cohort data, or more feasibly from case-control studies.

2.2. *Baseline Hazard,* $\mathbf{h_1(t)}$

The baseline age-specific hazard $h_1(t)$ is the age-specific breast cancer incidence rate for women whose risk factors were all at the lowest (baseline) level. Follow-up data from cohorts yield an estimate of the composite age-specific hazard rate $h^*_1(t)$ that reflects a mixture of women with various risk factor combinations. Gail et al. estimated $h_1(t)$ from $h_1(t)=h^*_1(t)\,[1-AR(t)]$, where $AR(t)$ is the attributable risk for women aged t. Gail et al. estimated $h^*_1(t)$ from BCDDP follow-up data and $1-AR(t)$ from BCDDP case-control data *(1)*.

The original model of Gail et al. *(1)* was designed to project all incident breast cancer, including *in situ* breast cancer. Estimating the absolute probability of invasive breast cancer to determine eligibility for the Breast Cancer Prevention Trial (BCPT) *(4)*, Anderson et al. used population-based invasive breast cancer incidence rates from the National Cancer Institute's (NCI) Surveillance, Epidemiology and End Result (SEER)

program to estimate $h^*_1(t)$ *(8,9)*. They estimated the corresponding attributable risk needed to compute $h_1(t)$ by combining the relative risk function $r(t)$ from Gail et al. *(1)* with information on the prevalence of risk factors in the general population in the Cancer and Steroid Hormone Study *(10)*. The resulting "model 2," which was described and studied by Costantino et al. *(9)*, very accurately predicted the numbers of invasive breast cancers actually observed in the BCPT.

The general strategy of estimating relative risk function $r(t)$ from a population-based case-control study and estimating baseline hazard $h_1(t)$ by combining an attributable risk estimate from population-based case-control data with SEER data on age-specific composite incidence, $h^*_1(t)$, is a powerful and practical approach that could be used to develop models to project absolute risk for other cancers, such as colon cancer.

2.3. The Hazard of Mortality From Causes Other Than the Disease of Interest, h2(t)

The third ingredient needed to compute absolute risk is the hazard of mortality, $h_2(t)$, from all causes of death except the disease of interest. Gail et al. *(1)* obtained $h_2(t)$ from general US mortality rates, and assumed that $h_2(t)$ did not depend on the covariates used to predict breast cancer incidence. In some applications, a risk factor such as a genetic mutation that increases risk for the disease of interest might also influence mortality from other causes. If such effects are known, they can be incorporated into formula number 5 in Gail et al. *(1)* for computing absolute risk by allowing $h_2(t)$, and the corresponding survival distribution, $S_2(t)$, to depend on covariates.

3. VALIDATING A MODEL FOR PROJECTING ABSOLUTE RISK

Costantino et al. *(9)* reviewed previous efforts to evaluate the original model of Gail et al. for projecting total breast cancer incidence ("model 1") and the modified model for projecting the risk of invasive breast cancer by Anderson and Redmond ("model 2"). Costantino et al. compared the relative risk function, which is common to both these models, with estimates of this function from independent case-control and cohort study data. The features of relative risk function were quantitatively consistent across studies, with few exceptions. Costantino et al. then assessed how well the observed number of breast cancers (O) agreed with the expected number (E) based on models 1 and 2. A model in which O and E are in good agreement is said to be well calibrated. Using data from the placebo arm of the BCPT, Costantino et al. found a ratio of E/O = 0.84 (95% confidence interval 0.73–0.97) for all breast cancer (model 1) and E/O = 1.03 (95% confidence interval 0.88–1.21) for invasive breast cancer (model 2). Thus, the models are well calibrated, especially model 2 for invasive breast cancer.

Rockhill et al. *(11)* confirmed the good calibration of these models in a larger set of data from the Nurses Health Study (NHS). However, they raised another important criterion for consideration, namely the discriminatory power of the model. Pointing out that distribution of absolute risk estimates in women in the NHS who ultimately developed breast cancer tended to be only modestly higher than distribution of risk prediction values in women who remained disease-free, they concluded that the ability of the model to discriminate women who will develop breast cancer from those who will not was modest. (The area under the receiver operating curve, AUC-ROC, was estimated as 0.58). Thus, despite these models being well calibrated and therefore useful in weighing risks and benefits, as in tamoxifen use *(3)*, considerable scope remains for improving the sensitivity, specificity, and discriminatory power of this model.

4. IMPROVING MODELS AND OTHER FUTURE DIRECTIONS

One way to improve the discriminatory power of a model is to include more powerful predictors. For example, one might try to incorporate information on mammographic density, on cytology from nipple aspirates, or on genetic mutations to improve the discriminatory power for identifying women who will develop breast cancer. Such an effort to improve discriminatory power is certainly worthwhile. However, an advantage of the current Gail model *(1)*, and of a model based only on a detailed family history of breast cancer by Claus et al. *(12)*, is that they only require interview data. Requiring information on more powerful (and invasive) predictors can restrict the range of application of the models.

Additional information must be obtained on the calibration of available models in various ethnic and racial groups. Work is needed to determine whether the relative risk function in Gail et al. *(1)*, which was derived from white women in the BCDDP, applies to other racial or ethnic groups. The version of model 2 available on the NCI's "Risk Disk" (http://bcra.nci.nih.gov/brc/) includes separate baseline hazard estimates for black women and Hispanic women, but more work is needed

to check the calibration of the model in racial and ethnic subgroups. Calibration must be also be checked of models such as those proposed by Claus et al. *(12)* and extensions of that model strongly based on the assumption that familial aggregation of breast cancer is due to an autosomal dominant mutation. Considerable evidence indicates that other factors contribute to such aggregation *(13)*.

Section 2.3. mentions a simple general strategy for estimating the absolute risk of a cancer by combining information on the relative risk function $r(t)$ and the attributable risk from a population-based case-control study with SEER data on age-specific composite incidence, $h^*_1(t)$. Ongoing work to develop a model to project the risk of colon or rectum cancer is based on this approach.

Models for projecting absolute risk to assist in medical decision-making will usually require weighing absolute risks of several health outcomes in the presence and absence of a proposed intervention, as when considering tamoxifen use *(3)* as mentioned in Section 1. An important need in this area is development of individualized models of absolute risk for each of the health endpoints that influence the intervention decision. Epidemiologists and risk modelers will need to take a broad view of the available data resources. In weighing risks and benefits, there is a pressing need to improve data sources for estimating absolute risks for a range of health outcomes.

REFERENCES

1. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst* 1989; 81:1879–1886.
2. Cornfield J. A method of estimating comparative rates from clinical data. Applications to cancer of the lung, breast, and cervix. *J Natl Cancer Inst* 1951;11:1269–1275.
3. Gail MH, Costantino JP, Bryant J, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. *J Natl Cancer Inst* 1999;91:1829–1846.
4. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998;90:1371–1388.
5. Gail MH. Sample size estimation when time-to-event is the primary endpoint. *Drug Info J* 1994;28:865–877.
6. Freedman L, Anderson G, Kipnis V, et al. Approaches to monitoring the results of long-term disease prevention trials: examples from the Women's Health Initiative. *Control Clin Trials* 1996;17:509–525.
7. Gail MH. The estimation and use of absolute risk for weighing the risks and benefits of selective estrogen receptor modulators for preventing breast cancer. *Ann NY Acad Sci* 2001; 949:286–291.
8. Anderson SJ, Ahnn S, Duff K. NSABP Breast Cancer Prevention Trial risk assessment program 2. NSABP Biostatistical Center Technical Report, August 14, 1992.
9. Costantino JP, Gail MH, Pee D, et al. Validation studies for models projecting the risk of invasive and total breast cancer incidence. *J Natl Cancer Inst* 1999;91:1541–1548.
10. Wingo PA, Ory HW, Layde PM, Lee NC. The evaluation of the data collection process for a multicenter, population-based, case-control design. *Am J Epidemiol* 1988;128: 206–217.
11. Rockhill B, Spiegelman D, Byrne C, et al. Validation of the Gail et al. model of breast cancer risk prediction and implications for chemoprevention. *J Natl Cancer Inst* 2001; 93:358–366.
12. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. *Cancer* 1994;73:643–651.
13. Claus EB, Schildkraut J, Iversen ES Jr, et al. Effect of BRCA1 and BRCA2 on the association between breast cancer risk and family history. *J Natl Cancer Inst* 1998;90:1824–1829.